CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022432Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: September 24, 2010

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Through: Claudia B. Karwoski, PharmD, Director
Division of Risk Management (DRISK)

From: Mary Dempsey BS, Risk Management Programs Coordinator, DRISK
Sharon Mills Sharon R. Mills, BSN, RN, CCRP, Patient Product Information Reviewer, DRISK

Subject: Risk Evaluation and Migitation Strategy (REMS) Review

Drug Name: H.P. Acthar® Gel (Repository Corticotropin)

Application Type/ Number: NDA 022432 and NDA 008372

Applicant/Sponsor: Questcor Pharmaceuticals, Inc.

OSE RCM #: 2010-1794

1 Background

The Division of Neurology Products (DNP) requested the Division of Risk Management (DRISK) review the H.P Acthar Gel (Repository Corticotropin) proposed Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 022432 and 008372 submitted by Questcor Pharmaceuticals, Inc. September 20, 2010.

2 Material Reviewed

- July 21, 2010 REMS Notification Letter
- September 20, 2010 Questcor Pharmaceuticals email containing REMS documents

3 Proposed REMS Elements

- Medication Guide
- Timetable for Submission of REMS Assessment

4 Discussion and Recommendations

July 21, 2010 DNP sent Questcor a REMS Notification letter that included the following language:

> "H.P. Acthar Gel (repository corticotrophin) was approved on April 29, 1952, for multiple indications. The label was later expanded to include multiple sclerosis (MS) in 1972. We are now adding the indication of infantile spasms in pediatric patients. The known risks of infections and blood pressure elevation in MS patients have also been identified as risks in the pediatric population based on clinical trial data. Additionally, the risk of adrenal insufficiency seen in other patient populations is an important potential serious adverse event in the pediatric population. The extension of the indication to pediatrics changes the risk benefit profile of H.P. Acthar Gel (repository corticotrophin) and is considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA. In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for H.P Acthar Gel (repository corticotropin) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, and blood pressure elevation.
>
> Your proposed REMS must include the following:
>
> - Medication Guide
> - Timetable for Submission of REMS Assessment "

DRISK comments on the REMS and Medication Guide are provided in Attachment A and B.

The comments regarding the Instructions for Use in the MG section "How should I give H.P. Acthar Gel to my child?" are collaborative DRISK and DMEPA comments.

We defer comment on your REMS assessment until you submit a full protocol and survey instrument.

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Acthar Gel. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Acthar Gel.
2. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

   Explain how often you perform non-respondent follow-up or reminders.

   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.
3. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
4. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
5. Ensure the sample is demographically representative of the population who use the drug.
6. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
7. List the inclusion criteria. For example, eligible caregiver respondents must be:
   - Age 18 or older
   - Currently administered Acthar Gel or administered the drug in the past 3 months

- Not currently participating in a clinical trial involving Acthar Gel
- Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

8. Explain how you administer surveys and the intended frequency.

   Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

   Explain how you train surveyors.

9. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).

10. Submit for review the introductory text used to inform respondents about the purpose of the survey.

    Tell potential respondents that their answers will not affect their ability to receive or take the drug, and that their answers and personal information will be kept confidential and anonymous.

11. Clarify in your methodology that respondents are eligible for one wave of the survey only.

12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

    According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

    Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Acthar Gel?" section of the Medication Guide.

    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

    Explain if and when any education will be offered for incorrect responses.

16. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

17. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with Acthar Gel. The Medication Guide is a paper handout that contains important information about the risks associated with use of Acthar Gel and how to use Acthar Gel safely. Medication Guides always include the title "Medication Guide" followed by the word Acthar Gel and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about Acthar Gel," "What is Acthar Gel," and "Who should not take Acthar Gel."

18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

    - Who gave you the Medication Guide for Acthar Gel? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain: _____
        d) I did not get a Medication Guide for Acthar Gel
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did you understand what you read in the Medication Guide?
        a) All,
        b) Most,
        c) Some,

d) None

- Did someone offer to explain to you the information in the Medication Guide?
    a) Yes, my doctor or someone in my doctor's office
    b) Yes, my pharmacist or someone at the pharmacy
    c) Yes, someone else – please explain: _____
    d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

19. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

    You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Please send these comments to the sponsor with a request to re-submit the entire REMS for approval.

15 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY J DEMPSEY
09/24/2010

CLAUDIA B KARWOSKI
09/24/2010
concur

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: September 10, 2010

From: Norman Hershkowitz, HD,PhD
Division of Neurology Products, HFD-120

Subject: Acthar Gel (NDA 22432) REMS (MedGuide) Modification Memo

This division initially decided that a MedGuide was required for all indications proposed for Acthar Gel. This was expressed in our initial REMS memo and request letter (7/12/10). Upon further discussions within the division, this decision was changed as we concluded that the REMS will only be necessary for the treatment of the newly labeled indication of Infantile Spasms. The reasons for this were expressed in our REMS revision letter of 9/1/10 to the Sponsor where we noted that we believed this infant population is a uniquely vulnerable group. This determination was based upon two factors unique to this indication, age and cognitive/behavioral compromise. Thus, all other planned labeled indications are for older children and adults; indeed the predominant use for this agent, outside of Infantile Spasms, would likely be solely for adults with Multiple Sclerosis1. As per our present version of the label, the indication of Infantile Spasms is the only indication that allows for the treatment of children younger then 2 years. In fact, children as young as only a few months will be treated. One of the most worrisome side effects of ACTH is the lowering of immunologic resistance. As a child's immature immune system is already considered compromised, as a result of its immaturity2, the additional immuno–suppressive effect of ACTH is thought to add an additional risk to this population. It is also noteworthy that while it is generally difficult to identify whether a child at this very young age is infected, the cognitive/behavioral deficits associated with Infantile Spasms make it even more difficult[2]. Moreover, Acthar Gel may suppress normal signs of infection such as fever. Thus, parents would have to be educated to these facts and highly vigilant for any potential signs of infection that may be limited to changes in behavior (e.g. decreased responsiveness or feeding). Moreover, parents of children must also be educated and advised to monitor other symptoms of Acthar Gel toxicity (e.g. post treatment adrenal insufficiency). The

1 The initial label was to have only two indications, Infantile Spasms and Multiple Sclerosis. DMEP was planning on removing approximately 50 other indications, for which ACTH has been rarely, if ever, used in recent clinical practice because safer and more effective alternatives now exist. These other indications were based upon a DESI determination. However, after further negotiations with the Sponsor, only about half of these will be removed from the label.

2 Rudolph's Pediatrics – 21st Ed. (2003), Chapter 13 by Julie A. Jaskiewicz "Fever Without Localizing Signs In Infants And Children."

parents must also be educated as to the importance of adequate follow up for their children so that other potential serious adverse events (hypertension) can be monitored. It is noteworthy that some members of the advisory committee strongly recommended some form of patient education as a part of a REMS.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN HERSHKOWITZ
09/22/2010

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs I
Division of Neurology Products

NDA/BLA #s:	22-432
Products:	H.P. Acthar Gel (repository corticotropin injection)
APPLICANT:	Questcor Pharmaceuticals, Inc.
FROM:	Russell Katz, M.D.
DATE:	June 7, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for H.P. Acthar Gel (repository corticotropin injection) to ensure that the benefits of the drug outweigh the risks of adrenal insufficiency, infections, sepsis, and blood pressure elevation. H. P. Acthar Gel (repository corticotropin injection) is presently approved for diagnostic testing of adrenocortical function and acute exacerbations of multiple sclerosis (MS). Questcor seeks approval for the use of H. P. Acthar Gel (repository corticotropin injection) to treat infantile spasms (IS). We have determined that a REMS is necessary for H. P. Acthar Gel (repository corticotropin injection) only for indications in which the drug is administered for a period exceeding five days (MS and IS), and not for the indication of diagnostic testing of adrenocortical function, in which single doses are administered. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States born with Infantile Spasms (IS) ranges from 1 per 2,250 to 1 per 6,000. Given that there are a little over 4,000,000 live births per year in the United States, there should be approximately 1,000 to 2,000 IS cases yearly. This incidence estimate is based upon a number of epidemiologic

articles published in peer-reviewed journals.[1] Even though H.P. Acthar Gel (repository corticotropin injection) is not presently indicated for use in the treatment of IS in the label, it is generally considered the treatment of choice in IS by many pediatric epileptologists. The Sponsor notes that there are presently (b) (4) to (b) (4) individual patients prescribed H. P. Acthar Gel (repository corticotropin injection) for IS each year. This accounts for (b) (4)% of IS patients. We suspect H. P. Acthar Gel (repository corticotropin injection) use will increase as a result of its approval and one may expect about (b) (4) patients treated yearly (approximately (b) (4)% to (b) (4)% of newly diagnosed cases).

The prevalence of MS in the United States is approximately 1 per 1000. A prevalence of 600,000 patients[2] in the United States has been estimated. H. P. Acthar Gel (repository corticotropin injection) is rarely used today to treat MS; however, a very small percentage of patients may still be treated with H. P. Acthar Gel (repository corticotropin injection).

B. Infantile Spasms is associated with frequent recurrent seizures (or spasms) and marked EEG (electroencephalogram) abnormalities. The disease is frequently associated with delayed development, permanent cognitive impairment and the occurrence of other seizure types upon maturation. Death may also occur. The long-term prognosis of infantile spasms is bleak. Fewer than 5% of patients are neurodevelopmentally normal. While there are no definitive data that treatment of the spasms will improve long term neurologic prognosis, there are limited data suggesting that this is the case.

MS is a chronic, often disabling disease that attacks the central nervous system (CNS). In Western societies, MS is second only to trauma as a cause of neurologic disability with onset in early to middle adulthood. MS can rapidly evolve to an incapacitating disease requiring profound lifestyle adjustments.[3] MS patients commonly have impaired ability to walk as well as weakness of the limbs, visual symptoms including decreased acuity and visual blurring, sensory symptoms including tingling, ataxia, bladder dysfunction, memory loss and impaired attention, depression, and fatigue. During acute exacerbations of MS, patients will lose neurologic function to varying degrees and may also be subject to injuries and other medical conditions associated with neurologic compromise (e.g., aspiration pneumonia and falls).

---

[1] Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. *J Child Neurol.* 1991;6(4):355-364; Cowan LD. The epidemiology of the epilepsies in children. *Ment Retard Dev Disabil Res Rev*. 2002;8(3):171-181.

[2] See Neurologic Clinics, Neuroepidemiology, Editor J.E Riggs, W.B. Saunders company, Philadelphia, 1996; Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohammed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurological disorders? Neurology 2007;68;326-337

[3] Harrison's Principles of Internal medicine – 17th Ed. (2008)

C. The efficacy of H. P. Acthar Gel (repository corticotropin) for the treatment of infantile spasms was studied in three controlled trials. Data reviewed by the division indicate that H. P. Acthar Gel (repository corticotropin) results in complete resolution of spasms and EEG abnormalities in a majority of patients as compared to an active control (87% in the Acthar Gel arm vs. 29% in the prednisone arm). While the data are not definitive, it is generally believed that prognosis improves with early diagnosis and treatment.

   While there is some evidence that this drug appears to limit the duration of the MS exacerbations, there is no evidence that it can reduce accrued disability in MS.

D. If approved, H. P. Acthar Gel (repository corticotropin) would be labeled in IS as a two-week course of treatment, followed by a two-week taper. At present there is no plan to label more then one such course of treatment.

   The drug is labeled in MS as a single two- to three-week course of treatment at the time of each exacerbation.

E. As a result of combined prospective analysis of clinical IS data and IS literature review, the Sponsor determined that the two most likely drug-related serious adverse events include infections and hypertension which were observed in 7.4% and 8.2% of patients, respectively. In the aforementioned database of 300 patients, it was noted that at least one infection led to a death. Another potential serious adverse outcome is that of adrenal insufficiency resulting from adrenocorticotropic hormone (ACTH) treatment. No cases of adrenal insufficiency were identified in the Sponsor's database, likely because of the careful dosing regimen that includes a slow down-titration. However, this remains an important potential serious adverse event and was also of great concern to the Peripheral and Central Nervous System Advisory Committee. Other less common but potentially serious adverse events included hypokalemia, hyperglycemia, and cardiomyopathy.

F. H.P. Acthar Gel (repository corticotropin injection) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of H.P. Acthar Gel (repository corticotropin). FDA has determined that H.P. Acthar Gel (repository corticotropin) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use H.P Acthar Gel (repository corticotrophin), and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be Medication Guide and a timetable for submission of assessments of the REMS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)
NDA-8372	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P. ACTHAR GEL
SAFETY-547	ORIG-1	NO FIRM	antiepileptic drugs

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B DAUGHERTY
07/06/2010

RUSSELL G KATZ
07/13/2010